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PATENT
55-301M

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent 4,604,463

Issued : August 5, 1986

To : Tadashi MIYASAKA, Seigo SAWADA, Kenichiro NOKATA, Eiichi SUGINO, and Masahiko MUTAI

Assignee : KABUSHIKI KAISHA YAKULT HONSHA

For : CAMPTOTHECIN DERIVATIVES AND PROCESS FOR PREPARING SAME

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

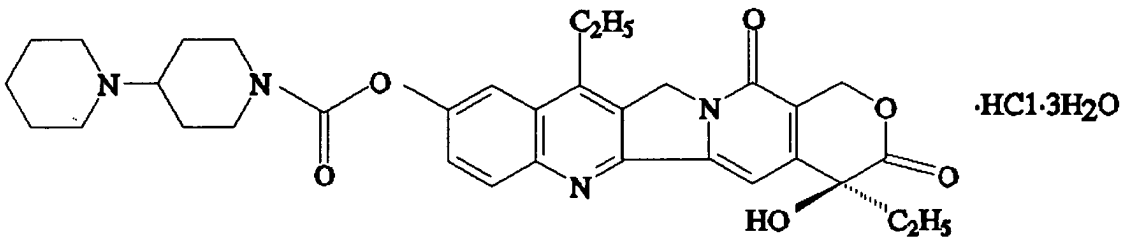
Commissioner of Patents
and Trademarks
Washington, D. C. 20231

Dear Sir:

Your applicant, KABUSHIKI KAISHA YAKULT HONSHA, represents that it is the assignee of the entire interest in and to Letters Patent for the United States 4,604,463 granted to Tadashi Miyasaka, Seigo Sawada, Kenichiro Nokata, Eiichi Sugino and Masahiko Mutai, on August 5, 1986 for CAMPTOTHECIN DERIVATIVES AND PROCESS FOR PREPARING SAME by virtue of an Assignment in favor of KABUSHIKI KAISHA YAKULT HONSHA recorded on July 5, 1984, at Reel 4301, Frames 948-949. Your applicant, acting through its duly authorized attorney whose power to act on behalf of applicant is filed simultaneously herewith (Exhibit 1), hereby submits this application for extension of patent term under 35 U.S.C. 156 by providing the following information required by 37 C.F.R. 1.740. For convenience, the information contained in this application will

be presented in a format and order which follows the requirements of 37 C.F.R. 1.740.

(1) The approved product CAMPTOSAR® (also referred to in some correspondence as "CPT-11") contains Irinotecan hydrochloride trihydrate, chemically described as (1) 7-Ethyl-10-[(4-piperidino-piperidino)carbonyloxy]-camptothecin hydrochloride trihydrate or (2) 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin hydrochloride trihydrate. Its structural formula is:



(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, § 512.

(3) The approved product CAMPTOSAR® received permission for commercial marketing or use under § 512 of the Federal Food, Drug and Cosmetic Act by virtue of a letter sent by the FDA dated June 14, 1996.

(4) The only active ingredient in CAMPTOSAR® is Irinotecan hydrochloride trihydrate, which has not been approved for

commercial marketing or use under § 512 of the Federal Food, Drug and Cosmetic Act prior to approval of NDA 20-571 by the Food and Drug Administration on June 14, 1996.

(5) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. 1.720(f), which period will expire on August 13, 1996.

(6) The complete identification of the patent for which a term extension is being sought is as follows:

Inventors: Tadashi Miyasaka, Seigo Sawada, Kenichiro Nokata, Eiichi Sugino and Masahiko Mutai

Patent No.: 4,604,463

Issue Date: August 5, 1986

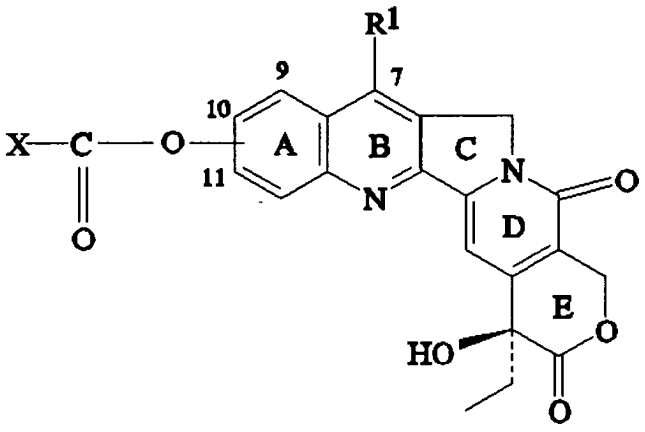
Expiration Date: July 5, 2004 (20 years from filing date)

(7) A true copy of the patent is attached as Exhibit 2.

(8) No Terminal Disclaimer, Certificate of Correction or Reexamination Certificate has been issued. Enclosed are copies of the receipts verifying payment of the maintenance fees in 1990 and 1994 (see Exhibit 3).

(9) U.S. Patent 4,604,463 claims the active compound of CAMPTOSAR®. Claims 1 and 20 of the patent claim camptothecin derivatives as follows:

Claim 1. Camptothecin derivatives of the formula:



(I)

wherein R^1 is a hydrogen atom, a halogen atom or an alkyl group with 1-4 carbon atoms and X is a chlorine atom or $-NR^2R^3$ where R^2 and R^3 are the same or different and each represents a hydrogen atom, a substituted or unsubstituted alkyl group with 1-4 carbon atoms or a substituted or unsubstituted group selected from the group consisting of cyclopentyl, cyclohexyl, N-methylpiperidyl-(4), 2-pyrrolidyl, phenyl, tolyl, xylyl, pyridyl-2 and 2-methylpyridyl-(4), with the proviso that when both R^2 and R^3 are the substituted or unsubstituted alkyl

groups, they may be combined together with the nitrogen atom, to which they are bonded, to form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine, 2-oxapyrrolidine, morpholine, thiomorpholine and 4-R^4 piperizine rings in which R^4 is a hydrogen atom, a substituted or unsubstituted alkyl group with 1-4 carbon atoms or a substituted or unsubstituted phenyl group and wherein the grouping -O-CO-X is bonded to a carbon atom located in any of the 9-, 10- and 11-positions in the ring A, and ammonium salts or alkali metal salts thereof.

Claim 20. Camptothecin derivatives according to claim 1, which are 10-[4-(piperidino)-1-piperidino]carbonloxy-7-R^1-camptothecins.

The claims read on the active compound of the approved product CAMPTOSAR®. The active ingredient of CAMPTOSAR®, Irinotecan hydrochloride trihydrate, is an antitumor compound. Irinotecan hydrochloride trihydrate is chemically described as (1) 7-Ethyl-10-[(4-piperidino-piperidino)carbonyloxy]-camptothecin hydrochloride trihydrate or (2) 7-Ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin hydrochloride trihydrate. This hydrochloride is water soluble and yields (1) 7-Ethyl-10-[(4-piperidino-piperidino)carbonyloxy]-camptothecin or (2) 7-Ethyl-10-

[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin, the active compound for exhibiting antitumor activity.

(10) Relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review are as follows:

An Investigational New Drug application (IND 35,229) for CPT-11 (Irinotecan hydrochloride trihydrate) was filed on August 3, 1990 and became effective on September 5, 1990.

A New Drug Application (NDA 20-571) for CAMPTOSAR® was submitted on December 28, 1995.

The New Drug Application (NDA 20-571) for CAMPTOSAR® was approved on June 14, 1996.

(11) As a brief description of the activities undertaken by applicant or applicant's representatives during the applicable regulatory review period, attached hereto is a chronology of the major communications between the applicant and the FDA from August 3, 1990 to June 14, 1996. (See Exhibit 4).

It will be noted that the initial IND Application for CPT-11 was filed on August 3, 1990 by G.H. Besselar Associates as authorized agent for KABUSHIKI KAISHA YAKULT HONSHA. The authorized representative for the IND was subsequently transferred to Theradex. Sponsorship of the IND was then later transferred to the Upjohn Company who subsequently filed the NDA for CAMPTOSAR®/CPT-11 on December 28, 1995. Finally, on June 11, 1996, the Upjohn Company changed its name to "The Pharmacia and Upjohn Company", which is now the owner of the NDA 20-571.

(12)(i) Applicant is of the opinion that U.S. Patent 4,604,463 is eligible for extension under 35 U.S.C. § 156 because it satisfies all requirements for extension as follows:

(a) 35 U.S.C. § 156(a) - U.S. Patent 4,604,463 claims as a new compound the active ingredient in CAMPTOSAR®.

(b) 35 U.S.C. § 156(a)(1) - U.S. Patent 4,604,463 has not expired before submission of this application.

(c) 35 U.S.C. § 156(a)(2) - The term of U.S. Patent 4,604,463 has never been extended under 35 U.S.C. § 156(e)(1).

(d) 35 U.S.C. § 156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. § 156(d) and the rules of the Patent and Trademark Office.

(e) 35 U.S.C. § 156(a)(4) - The product CAMPTOSAR® has been subjected to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. § 156(a)(5)(A) - The commercial marketing or use of the product CAMPTOSAR® after the regulatory review period is the first permitted commercial marketing or use under the provision

of the Federal Food, Drug and Cosmetic Act (i.e. Section 512) under which such regulatory review period occurred.

(g) 35 U.S.C. § 156(c)(4) - No other patent has been extended for the same regulatory review period for the product CAMPTOSAR®.

(12)(ii) The length of the extension of patent term of U.S. Patent 4,604,463 claimed by Applicant is 1,139 days or 3.12 years. The length of the extension was determined pursuant to 37 C.F.R. § 1.778 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(4)(B) began on September 5, 1990 and ended June 14, 1996, which is a total of 2,109 days or 5.78 years, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. § 156(g)(4)(B)(i), the "Testing Period", began on September 5, 1990 and ended on December 28, 1995, which is 5.32 years or 1,940 days.

(2) The period of review under 35 U.S.C. § 156(g)(4)(B)(ii), the "Approval Period", began on December 28, 1995 and ended on June 14, 1996, which is 0.46 years or 169 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph (12)(ii)(a) above (2,109 days) less:

(1) The number of days in the regulatory review period which were on or before the date on which the patent issued (August 5, 1986) which is zero (0) days; and

(2) The number of days during which applicant did not act with due diligence, which is zero (0) days; and

(3) One-half the number of days determined in subparagraph (12)(ii)(a)(1) after the patent issued (one-half of 1,940 days) which is 970 days;

(c) The number of days as determined in subparagraph (12)(ii)(b) (1,139 days or 3.12 years) when added to the original term of the patent (July 5, 2004) would result in the date August 15, 2007;

(d) Fourteen (14) years when added to the date of NADA approval June 14, 1996 would result in the date June 14, 2010;

(e) The earlier date as determined in subparagraphs (12)(ii)(c) and (12)(ii)(d) is August 15, 2007.

(f) Since U.S. Patent 4,604,463 issued after September 24, 1984, the period of extension may not exceed five (5) years. Five (5) years when added to the original expiration date of the patent (July 5, 2004) would result in the date of July 5, 2009.

(g) The earlier date as determined by subparagraph (12)(ii)(e) and (12)(ii)(f) is August 15, 2007.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee under 37 C.F.R. § 1.20(j) for receiving and acting upon this application is attached as a check in the amount of $1,060.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 02-2448.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

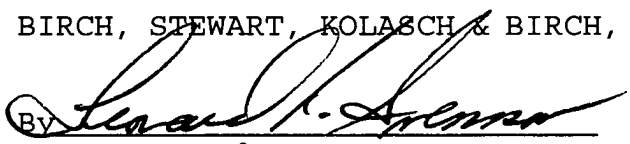
Leonard R. Svensson
BIRCH, STEWART, KOLASCH & BIRCH, LLP
P. O. Box 747
Falls Church, VA 22040-0747
Phone: (703) 205-8000
Fax: (703) 205-8050

(16) Enclosed is a certification that the application for extension of patent term under 35 U.S.C. § 156 including its attachments and supporting papers is being submitted as one original and a duplicate copy thereof (Exhibit 5).

(17) The requisite Declaration pursuant to 37 C.F.R. § 1.740(b) is attached (Exhibit 6).

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By 
Leonard R. Svensson
Reg. No. 30,330

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

Dated: August 12, 1996

Attachments:
Power of Attorney (Exhibit 1)
U.S. Patent 4,604,463 (Exhibit 2)
Copies of Receipts for Maintenance Fees (Exhibit 3)
Chronology of Regulatory Review Period (Exhibit 4)
Certification of Copies of Application Papers (Exhibit 5)
Declaration pursuant to 37 C.F.R. § 1.740(b) (Exhibit 6)

LRS/pw